15 September 2016
EMA/682762/2016
Human Medicines Evaluation Division

Assessment report for paediatric studies submitted according to Article 46 of the Regulation (EC) No 1901/2006

Bexsero

meningococcal group B vaccine (rDNA, component, adsorbed)

Procedure no: EMEA/H/C/002333/P46/020 & 021

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

Table of contents

1. Introduction

The clinical study reports of studies V102_03 and V102_03E1 are submitted in accordance with Article 46 of Regulation (EC) No 1901/2006, as amended. These studies were conducted as part of the development program of the investigational meningococcal combination vaccine MenABCWY, intended to protect against the five most common *Neisseria meningitides* serogroups (A, B, C, W and Y) responsible for invasive meningococcal disease worldwide. MenABCWY combination vaccine is based upon two established GSK vaccine components, Menveo and Bexsero.

Bexsero was used in study V102_03 as a comparator vaccine, while in study V102_03E1 was evaluated the antibody persistence at 24 months after vaccination performed in study V102_03.

The MAH has also submitted the V102_03 Erratum to the CSR dated 15 December 2014. This Erratum was stated to be issued in order to correct some minor transcription errors affecting the original CSR, that have no impact on any of the analyses and interpretations of the study results presented in the original CSR.

The MAH stated that the submitted paediatric studies do not influence the benefit/risk for Bexsero and therefore no amendments to the product information have been identified.

A short critical expert overview has also been provided.

1.1. Steps taken for the assessment

Submission date:	23 June 2016
Start of procedure:	16 June 2016
Rapporteur's preliminary assessment report circulated on:	8 August 2016
Rapporteur's updated assessment report circulated on:	n/a
PRAC adoption of conclusions:	2 September 2016
CHMP adoption of conclusions:	15 September 2016

2. Summary of data submitted

The best option for the control of meningococcal disease would be the use of effective vaccines against all 5 of the most common serogroups (A, B, C, W-135, and Y) responsible for invasive meningococcal disease in humans. Based upon its extensive clinical experience with the MenACWY vaccine and with the rMenB (with or without OMV) vaccine, Novartis is developing such a combination vaccine; this study is part of that effort.

A phase 1 study (V102P1) evaluating the safety, tolerability, and immunogenicity of several formulations of a meningococcal ABCWY (MenABCWY) combination vaccine administered to healthy adults has been completed. A phase 2 study (V102_02) evaluating the safety, tolerability, and immunogenicity of 4 different MenABCWY vaccine formulations, with or without OMV, and with different amounts of recombinant proteins in healthy adolescents (aged 11 through 18 years), has also been completed.

The primary phase 2 study (V102_03) was designed to evaluate 2 MenABCWY formulations (MenABCWY+ OMV and MenABCWY+¼OMV) given at a 0, 2 month schedule in order to demonstrate that the safety and immunogenicity of the combination vaccine are at least comparable to that of the licensed vaccine, Menveo, in adolescents and adults aged 10-25 years. Study results from V102_03 were used to select the final MenABCWY formulation, ABCWY+OMV to bring forward into clinical development.

The V102_03E1 study is an extension of primary phase 2 study V102_03, conducted in healthy subjects who were 10 to 25 years of age at the time of participation in the parent study. The aim of the extension study was to evaluate the immunogenicity and safety of a booster dose of the same formulation of MenABCWY vaccine received in the parent study V102_03, administered approximately 24 months after completion of the primary vaccination series in V102_03. Antibody persistence at 24 and 36 months after the primary vaccination series and 12 months after the booster dose was also to be evaluated in study subjects.

Scientific Discussion

2.1. Information on the development program

Study V102_03 was a phase 2, observer blinded, controlled, randomized multi-center study in adolescents and young adults to evaluate safety and immunogenicity of two different rMenB with OMV + MenACWY combination vaccination formulations.

Study V102_03E1 was a phase 2, observer-blind, placebo-controlled, randomized, multi-center extension study to evaluate the safety and immunogenicity of a booster dose of a MenABCWY vaccine administered 24 months following the primary series to adolescents and young adults who participated in V102_03.

2.2. Information on the pharmaceutical formulation used in the study

The investigational formulations (MenABCWY+OMV and MenABCWY+qOMV) contained the same quantity of oligosaccharides of *N. meningitidis* serogroups A, C, W-135, and Y (conjugated to CRM-197 protein) and the same quantity of serogroup B fusion proteins 936-741, 287-953, and 961c, but differed in the amount of outer membrane vesicle (OMV) component, containing either a ‘full’ dose of 25 µg, or a ‘quarter dose’ of 6.25 µg.

The commercially available formulations of Bexsero and Menveo were used.

2.3. Clinical aspects

Introduction

Meningococcal meningitis and sepsis are diseases that can result in death within hours, despite the availability of effective antibiotics. The diseases are caused by *Neisseria meningitidis,* a gram-negative, encapsulated bacterium classified into 5 major pathogenic serogroups (A, B, C, Y, and W-135) on the basis of the chemical composition of distinctive capsular polysaccharides. The reported annual incidence of meningococcal disease is highly variable both geographically and temporally within the same regions. In the United States, an estimated 800 to 1,200 cases of meningococcal disease occurred annually from 2005 through 2011, representing an incidence of 0.3 cases per 100,000 population (CDC, 2013). In Europe, more than 9600 cases were reported in 2008 and 2009, representing an incidence of 0.9 to 1.0 per 100,000 persons per year during that time; the incidence in individual European countries during the same period ranged from 0.3 to 3.5 cases per 100,000 population (ECDC, 2011). Much higher rates are reported from the “meningitis belt” of Africa where

incidence rates were >1,000 per 100,000 persons per year during large outbreaks (LaForce et al., 2009). The case-fatality rate ranges from 5% to 15%, and up to 25% of survivors are left with neurological sequelae, limb loss, or hearing loss. The disease is most common in children and young adults.

Based upon the successful development of conjugate vaccines designed to prevent disease caused by *Haemophilus influenzae* type b, *Streptococcus pneumoniae*, and *Neisseria meningitidis* serogroup C, Novartis Vaccines and Diagnostics has developed a conjugate MenACWY vaccine (Menveo®). This vaccine contains capsular oligosaccharides from *N. meningitidis* serogroups A, C, W-135, and Y conjugated to a protein carrier, CRM197 (a nontoxic mutant of diphtheria toxin). MenACWY vaccine has been shown to be generally well tolerated and immunogenic in several age groups (Black et al., 2010; Jackson et al., 2009), and received marketing authorization in both the US and the European Union in early 2010.

In contrast, prevention of serogroup B disease by the use of vaccines containing serogroup B capsular polysaccharide has been problematic because the B polysaccharide is poorly immunogenic and could theoretically elicit autoantibodies because it is identical to a carbohydrate moiety that is widely distributed in the human body. As a result, research has focused on outer membrane proteins of meningococci as potential vaccine candidates. Serogroup B vaccines based on outer membrane vesicles containing proteins, referred to as OMV, have been developed from epidemic serogroup B strains and used to control outbreaks in several countries, i.e., Norway , Brazil, Cuba, New Zealand (Holst et al., 2009; Noronha et al., 1995). Novartis Vaccines and Diagnostics has developed a multi-component recombinant protein meningococcal serogroup B vaccine containing OMV (referred to as rMenB+OMV) with broad coverage. This vaccine (Bexsero®) received marketing authorization from the European Union in January 2013, from Australia in August 2013, and from Canada in December 2013.

Clinical studies

Description

Study V102_03 was a phase 2, observer blinded, controlled, randomized multi-center study in adolescents and young adults to evaluate safety and immunogenicity of two different rMenB with OMV + MenACWY combination vaccination formulations.

Study V102_03E1 was a phase 2, observer-blind, placebo-controlled, randomized, multi-center extension study to evaluate the safety and immunogenicity of a booster dose of a MenABCWY vaccine administered 24 months following the primary series to adolescents and young adults who participated in V102_03.

Methods

Study V102_03

Objectives

Immunogenicity

Primary

- To demonstrate immunologic noninferiority of 2 doses of 2 different formulations of MenABCWY vaccine1 to a single dose of MenACWY vaccine2, as measured by the percentage of subjects with hSBA seroresponse against *N. meningitidis* serogroups A, C, W-135, and Y, at 30 days after the second vaccination, in healthy adolescents and young adults aged 10 through 25 years.

- To identify the optimal formulation of MenABCWY vaccine compared with a single dose of Menveo (MenACWY) and with 2 doses of **rMenB+OMV** in healthy adolescents and young adults aged 10 through 25 years, based on the overall desirability index.

  The overall desirability index is based on immunogenicity parameters (GMT ratios against *N. meningitidis* serogroups A, C, W-135, and Y and serogroup B test strains at 30 days after the second vaccination) and reactogenicity parameters (percentages of doses associated with severe local and severe systemic solicited AEs following any vaccination).

Secondary

- To estimate the immunogenicity of 2 doses of 2 different formulations of MenABCWY vaccine as measured by the percentage of subjects with hSBA ≥ 1:5 and hSBA ≥ 1:8 against strains of *N. meningitidis* serogroup B, at 30 days after the second vaccination.
- To compare the immunogenicity of 2 doses of 2 different formulations of MenABCWY vaccine with that of a single dose of Menveo (MenACWY), as measured by the percentage of subjects with hSBA ≥ 1:8 and hSBA GMTs against *N. meningitidis* serogroups A, C, W-135, and Y, at 30 days after the second vaccination.
- To compare the immunogenicity of 2 doses of 2 different formulations of MenABCWY vaccine with 2 doses of **rMenB+OMV** as measured by the percentage of subjects with hSBA ≥ 1:5, hSBA ≥ 1:8, 4-fold rise, and hSBA GMTs against strains of *N. meningitidis* serogroup B, at 30 days after the second vaccination.

CHMP comment:

The focus will be on Bexsero in the present procedure. Therefore, results for all the objectives described above will not be evaluated in this report.

Safety

To evaluate the safety of 2 doses of each of the 2 formulations of MenABCWY vaccine.

Study design

This was a phase 2, observer-blinded, controlled, randomized, multicenter study in healthy adolescents and young adults to evaluate the safety and immunogenicity of 2 different MenABCWY vaccine formulations. Subjects aged 10 through 25 years were to be enrolled in this study.

A total of approximately 480 healthy subjects were to be randomized in a 1:1:1:1 ratio to 1 of the 4 groups described below to receive the vaccinations:

- Study group ABCWY+OMV received the MenABCWY+OMV vaccine formulation (containing a 'full dose' of outer membrane vesicles [OMV]) on a 0,2-month schedule.
- Study group ABCWY+qOMV received the MenABCWY+qOMV vaccine formulation (containing a 'quarter dose' of OMV) on a 0,2-month schedule.
- Study group rMenB+OMV received the **rMenB+OMV** vaccine (containing a 'full dose' of OMV) on a 0,2-month schedule.
- Study group Placebo/MenACWY received a single dose of placebo and a single dose of MenACWY vaccine, respectively, on a 0,2-month schedule.

Subjects were to have 2 blood draws (20 mL [±5 mL] each) during the study period; before the first vaccination, on day 1, and 30 days following the second vaccination, on day 91 (-4/+14 days).

Endpoints

Immunogenicity

- Percentage of subjects with seroresponse to *N. meningitidis* serogroups A, C, W-135, and Y;
- Percentage of subjects with hSBA ≥ 1:8 for *N. meningitidis* serogroups A, C, W-135, and Y;
- Percentage of subjects with hSBA ≥ 1:5, hSBA ≥ 1:8, and 4-fold increase for *N. meningitidis* serogroup B test strains;
- GMTs for *N. meningitidis* serogroups A, C, W-135, and Y and serogroup B test strains.

The following serogroup B test strains were used in this study; each strain was selected to test the antibody response to a single antigen(antigen specificity is shown in parentheses): M14459 (fHbp), M07-0241084 (NHBA), M01-0240364 (NadA), and NZ98/254 (PorA).

Safety and reactogenicity endpoints

- Local solicited reactions (i.e., pain, erythema, and induration), systemic solicited reactions (i.e., chills, nausea, fatigue, myalgia, arthralgia, loss of appetite, headache, rash, and fever [defined as body temperature ≥38°C]), unsolicited AEs, and SAEs were to be collected daily for 7 days after each vaccination;
- From day 8 through day 91 all unsolicited AEs, SAEs, and concomitant medications were to be collected.
- From day 92 (31 days following vaccination 2) through day 241 (180 days following vaccination 2) only medically attended AEs, SAEs, and AEs leading to withdrawal from the study were to be collected.

Composite endpoints (immunogenicity and reactogenicity)

- The overall desirability index is defined as the weighted geometric mean of individual desirability indexes based on the following immunogenicity and reactogenicity parameters:
- Between-group ratios of hSBA GMTs, adjusted for prevaccination titer and center, against *N. meningitidis* serogroups A, C, W-135, and Y at 30 days after the second vaccination: ABCWY+OMV group vs. Placebo/ACWY group and ABCWY+qOMV group vs. Placebo/ACWY group;
- Between-group ratios of hSBA GMTs, adjusted for prevaccination titer and center, against *N. meningitidis* serogroup B test strains at 30 days after the second vaccination: ABCWY+OMV group vs. rMenB+OMV group and ABCWY+qOMV group vs. rMenB+OMV group;
- Percentage of doses associated with severe local solicited AEs within 3 days following the vaccination for the ABCWY+OMV and ABCWY+qOMV groups;
- Percentage of doses associated with severe systemic solicited AEs within 3 days following the vaccination for the ABCWY+OMV and ABCWY+qOMV groups.

Statistical methods

Noninferiority of immune response against N.meningitidis serogroups A, C, W-135, and Y

The null hypothesis associated with the first primary immunogenicity objective was based on noninferiority of 2 doses of 2 different formulations of MenABCWY vaccine to a single dose of MenACWY, as measured by the percentage of subjects with hSBA seroresponse against *N. meningitidis* serogroups A, C, W-135, and Y, at 30 days after the second vaccination. Two doses of MenABCWY vaccine were considered noninferior to a single dose of MenACWY if the lower limit of the 2-sided 95% confidence interval (CI) around the difference between study groups (ABCWY – Placebo/ACWY), in percentage of subjects with seroresponse, was > −10% for each of the A, C, W-135, and Y serogroups.

Identification of the optimal formulation of MenABCWY vaccine

No hypothesis testing was associated with this second primary objective. The assessment was based on the ranks obtained after computation of the overall desirability index (Derringer & Suich, 1980) for each formulation, according to predefined weighting models for combining each of the 10 parameters chosen for this purpose. These parameters were, for immunogenicity, GMT ratios against *N. meningitidis* serogroup A, C, W-135, and Y (ABCWY+OMV group or ABCWY+qOMV group vs. Placebo/ACWY group) and against the 4 serogroup B test strains (ABCWY+OMV group or ABCWY+qOMV group vs. rMenB+OMV group) at 30 days after the second vaccination, and for reactogenicity, percentage of doses associated with severe local and with severe systemic solicited AEs following any vaccination. The desirability function was defined on a scale between 0 and 1 (0 for undesirable response and 1 for highly desirable response). Desirability functions for the A, C, W-135, and Y serogroups, for serogroup B test strains, and for local and systemic reactogenicity are presented in Figure 2-1.

Results

Immunogenicity

Of 484 enrolled subjects, 480 subjects (99%) received at least 1 study vaccination. The demographic variables and baseline characteristics were well balanced across study groups. The mean age of the subjects was 15.0 (±4.9) years and the majority (61%) were Caucasian.

Results involving Bexsero will be presented below:

The secondary immunogenicity objectives were to assess and compare the immunogenicity of 2 doses of 2 different MenABCWY vaccine formulations with a single dose of MenACWY, and with 2 doses of rMenB+OMV, using various endpoints, at 30 days after the second vaccination:

- As measured by percentages of subjects with hSBA ≥1:5 and hSBA ≥1:8 against serogroup B test strains, both the MenABCWY+OMV and MenABCWY+qOMV formulations induced a robust immune response against each of the 4 strains. No notable differences between the formulations were observed. The rMenB+OMV vaccine induced a higher immune response than did either MenABCWY formulation.
- As measured by percentages of subjects with 4-fold increase in hSBA titer against serogroup B test strains at 30 days after the second vaccination, the MenABCWY+OMV and MenABCWY+qOMV formulations induced comparable responses against all 4 strains. The percentages of subjects with such an increase were higher in the rMenB+OMV group than in either ABCWY group for each of the test strains.
- As measured by hSBA GMTs against serogroup B test strains, there was no meaningful difference between the ABCWY+OMV and ABCWY+qOMV groups, however, a trend toward higher postvaccination GMTs with the MenABCWY +OMV formulation was observed for 3 of the 4 test strains (NHBA, NadA, and PorA). The rMenB+OMV vaccine induced a higher immune response than did either MenABCWY formulation for all 4 serogroup B test strains (except for the fHbp strain in the ABCWY+qOMV group).

Exploratory immunogenicity analysis against 2 additional serogroup B test strains (strain 44/76-SL and strain 5/99) which express antigens identical in amino acid sequence to vaccine antigens fHbp and NadA, respectively, and are high expressers of these antigens, was also performed to further characterize the immune response at 30 days after the second vaccination:

- Both MenABCWY formulations induced a robust immune response against both of these test strains, as measured by percentage of subjects with hSBA ≥1:5 and percentage of subjects with hSBA ≥1:8. Results were comparable across both ABCWY groups and the rMenB+OMV group: 98% to 100% of subjects in all 3 groups had hSBA ≥1:5 and hSBA ≥1:8 against both test strains.

- GMTs and GMRs (postvaccination/baseline) also indicated that both MenABCWY formulations induced a robust immune response against both of the 44/76-SL and 5/99 test strains. No notable difference overall was seen between the MenABCWY formulations. GMTs against both serogroup B test strains were higher in the rMenB+OMV group.

CHMP comment:

Both of the tested MenABCWY formulations induced robust immune responses to the serogroup B test strains. However, the responses following vaccination with Bexsero were higher, which is also reflected in the desirability index shown in Table 1.

Table 1. Desirability index

	Endpoint Values				Transformed Values (Individual Desirability Index)	
	ABCWY+ OMV	ABCWY+ qOMV	rMenB+ OMV	Placebo/ ACWY	ABCWY+ OMV	ABCWY+ qOMV
	---------- Immunogenicity ----------					
	---------- GMT[a] ----------				Between-group GMT ratio	
ACWY serogroup					**Ratio vs. Pbo/ACWY**	
A	**71**	**76**	67	**44**	1.590	1.707
C	**228**	**182**	24	**50**	4.523	3.617
W-135	**236**	**279**	262	**66**	3.596	4.252
Y	**151**	**131**	2.61	**52**	2.902	2.503
B test strain					**Ratio vs. rMenB+OMV**	
fHbp (M14459)	**9**	**12**	**16**	1.18	0.554	0.723
NHBA (M07-0241084)	**7.06**	**6.3**	**12**	2.12	0.599	0.535
NadA (M01-0240364)	**56**	**48**	**117**	1	0.479	0.408
PorA (NZ98/254)	**8.54**	**7.94**	**18**	1.08	0.464	0.432
	Reactogenicity (% of doses associated with severe solicited AE through day 3)					
Local solicited AEs	**18%**	**17%**	22%	10%	18	17
Systemic solicited AEs	**12%**	**9%**	14%	6%	12	9

Source: Table 14.2.1.8; Table 14.2.1.9; Table 14.2.1.9.1; Table 14.2.1.10; Table 14.2.1.11.1.
Abbreviations: AE = adverse event.
Note: Endpoint values in bold were used to determine the individual desirability indexes in the middle columns.
[a] GMTs are adjusted for group, center, and prevaccination titer.
[b] These values were calculated using the desirability function originally defined for PorA; the desirability indexes calculated from the original NadA desirability function were 0.000 for each formulation (details in section 9.8).

Safety

Among 484 subjects in the enrolled population, 480 (99%) subjects were exposed to a study vaccine. Across all study groups, 99% of enrolled subjects provided unsolicited AE data, and 90% and 87% of enrolled subjects provided solicited AE data after the first and second vaccinations, respectively.

Table 2-6: Number (%) of Subjects With At Least One Reactogenicity Sign Reported From 6 Hours Through Day 7, by Vaccination: Solicited Safety Sets

	ABCWY+OMV	ABCWY+qOMV	rMenB+OMV	Pbo/ACWY
Vaccination 1				
	N=107	**N=109**	**N=114**	**N=96**
Any	98 (92%)	94 (86%)	106 (93%)	60 (63%)
Local	96 (90%)	92 (84%)	105 (92%)	36 (38%)
Systemic	71 (66%)	76 (70%)	71 (62%)	45 (47%)
Other	25 (23%)	31 (28%)	23 (20%)	8 (8%)
Vaccination 2				
	N=102	**N=105**	**N=109**	**N=93**
Any	87 (85%)	83 (79%)	93 (85%)	59 (63%)
Local	84 (82%)	77 (73%)	91 (83%)	49 (53%)
Systemic	60 (59%)	57 (54%)	71 (65%)	43 (46%)
Other	21 (21%)	14 (13%)	23 (21%)	10 (11%)
Any Vaccination				
	N=108	**N=111**	**N=115**	**N=99**
Any	102 (94%)	100 (90%)	109 (95%)	76 (77%)
Local	100 (93%)	97 (87%)	109 (95%)	60 (61%)
Systemic	85 (79%)	83 (75%)	85 (74%)	60 (61%)
Other	35 (32%)	38 (34%)	36 (31%)	17 (17%)

Source: Table 14.3.1.1.1; Table 14.3.1.1.2.
Note : 'Other' refers to other indicators of reactogenicity, specifically, subject stayed home due to reaction or subject took medication to prevent or treat fever or other symptoms.

CHMP comment:

The frequencies of local and systemic solicited adverse events (AEs) after the first study vaccination were higher in the rMenB-containing vaccine groups than in the Placebo/ACWY group. It is previously known that Bexsero has a higher reactogenicity than certain other vaccines, and therefore the results are in line with what is already known regarding Bexsero.

Frequencies of solicited AEs were generally lower after the second vaccination than after the first vaccination in the ABCWY+OMV, ABCWY+qOMV, and rMenB+OMV groups. The most common local solicited AE was injection site pain, reported after the first vaccination by 84% to 90% of subjects in the ABCWY+OMV, ABCWY+qOMV, and rMenB+OMV groups and 27% of subjects in the Placebo/ACWY group, and after the second vaccination by 73% to 83% and 42%, respectively.

The most commonly reported systemic solicited AEs after the first vaccination were myalgia (49% to 52% of subjects in rMenB-containing vaccine groups vs. 26% of subjects in the Placebo/ACWY group). Also, the most commonly reported severe systemic solicited AEs in rMenB-containing groups were myalgia (3% to 13% of subjects after any vaccination). The majority of these reactions were of short duration. Myalgia is a previously known AE after vaccination with Bexsero and is already included in the SPC section 4.8.

Table 2-7: Number (%) of Subjects With At Least One Unsolicited AE After Vaccination: Unsolicited Safety Set

	ABCWY+OMV	ABCWY+qOMV	rMenB+OMV	Pbo/ACWY
	N=120	N=120	N=120	N=109
Any AE within 30 days of first vaccination (days 1–30)	21 (18%)	28 (23%)	33 (28%)	20 (18%)
At least possibly related	8 (7%)	8 (7%)	12 (10%)	4 (4%)
Any AE within 30 days of second vaccination (days 61–91)	9 (8%)	5 (5%)	9 (8%)	7 (7%)
At least possibly related	2 (2%)	1 (1%)	1 (1%)	1 (1%)
Any AE from days 1–91	51 (43%)	55 (46%)	66 (55%)	50 (46%)
At least possibly related	13 (11%)	10 (8%)	16 (13%)	6 (6%)
Any AE from days 1–241	56 (47%)	60 (50%)	71 (59%)	60 (55%)
Medically attended AEs[a]	26 (22%)	24 (20%)	30 (25%)	31 (28%)
At least possibly related	0	0	0	0
SAEs (days 1–241)	2 (2%)	2 (2%)	1 (1%)	3 (3%)
At least possibly related	0	0	0	0
AEs leading to premature withdrawal (days 1–241)	0	0	2 (2%)	0
Deaths (days 1–241)	0	0	0	0

Source: Table 14.3.1.1.19; Table 14.3.1.1.20; Table 14.3.1.1.21; Table 14.3.1.1.23; Table 14.3.1.1.27; Table 14.3.1.1.31; Table 14.3.1.1.32.1; Table 14.3.1.1.32.1; Table 14.3.1.1.33; Table 14.3.1.1.41; Table 14.3.1.1.43.1; Table 14.3.1.1.44; Table 14.3.1.1.46.

[a] Medically attended AEs includes SAEs and AEs leading to withdrawal from the study.

CHMP comment:

The percentages of subjects with possibly related unsolicited AEs reported during the entire study period (days 1 through 241) were 11% and 8% in the ABCWY+OMV and ABCWY+qOMV groups, respectively, 13% in the rMenB+OMV group, and 6% in the Placebo/ACWY group. Injection site induration, injection site pain, and headache were the only AEs reported by more than 2% of subjects in any study group for whom the investigator considered the AE possibly or probably related.

Two subjects, both in the Bexsero group, reported an AE that led to premature withdrawal. One subject (11/040) reported lymphadenopathy, considered possibly related, on day 6 after the first vaccination. The other subject (24/066) reported convulsion, considered not related, on day 60 after the first vaccination. The subject who reported lymphadenopathy had a slightly raised temperature abd a generalized lymphaenopathy according to the listing of comments. It is not possible to conclude whether these symptoms actually were due to vaccination or something else, including infection.

A total of 10 SAEs were reported by 9 subjects (1% to 3% of subjects in each study group). None of the SAEs was considered related to study vaccine.

No new safety concerns regarding Bexsero were identified based on the study results presented from this study.

Erratum to the V102_03 SCR

The rationale for this erratum to the full clinical study report (CSR) dated 17 DEC 13 (presented above) was the identification of minor transcription errors in the study disposition flowchart (Figure 10.1-1 on page 96 of the original e-published CSR), and errors in the titles of four appendices in section 16.0 (Correct titles are given in V102_03_10DEC14_app(erratum). In addition, one misattribution of gender and two wrongly recorded dates of birth have been identified in the study database. These errors are described below.

CHMP comment:

It is agreed that the errors appear to have no impact on any of the analyses and interpretations of the study results. Therefore, the erratum is considered acceptable.

Study V102_03E1

Objectives

Immunogenicity

Primary

- To evaluate the immune response against *N meningitidis* serogroups A, C, W and Y strains as measured by percentage of subjects having seroresponse2 at day 30 following administration of a booster dose of MenABCWY in subjects who previously received the same vaccine formulation in study V102_03.
- To evaluate the immune response against *N meningitidis* serogroups B strains as measured by percentage of subjects having high-throughput human serum bactericidal assay (HT-hSBA) titers ≥1:5 at Day 30 following administration of a booster dose of MenABCWY in subjects who previously received the same vaccine formulation in study V102_03.

Secondary

- To evaluate the immune response against *N meningitidis* serogroups A, C, W and Y and serogroup B strains at day 30 following the booster vaccination with MenABCWY vaccine in subjects who previously participated in V102_03.
- To evaluate the antibody persistence against *N meningitidis* serogroups A, C, W and Y and serogroup B strains at 24 and 36 months after the primary vaccination series in subjects who previously participated in V102_03.
- To evaluate the antibody persistence against *N meningitidis* serogroups A, C, W and Y and serogroup B strains 12 months following the booster vaccination with MenABCWY vaccine in subjects who previously participated in V102_03.

CHMP comment:

Similarly as for the base study (V102_03), the focus will be on Bexsero. Therefore, results for all the objectives described above will not be evaluated in this report.

Safety

- To evaluate the safety and reactogenicity of the study vaccines.
- To assess safety of the study vaccines in terms of new onset of chronic diseases (NOCD) reported since completion of the primary study up to day 1 in study V102_03E1.

Study design

This is a phase 2, observer-blinded, placebo-controlled, randomized, multicenter extension study in healthy adolescents and young adults that participated in the parent study, V102_03.

The subjects were randomized to one of the study groups after obtaining informed consent from subjects or their legal guardian.

In the parent study V102_03, subjects were randomized in 4 vaccine groups. In the present extension study these groups were further randomized to receive either one of the MenABCWY vaccine formulations or a placebo approximately 24 months after the last vaccination was completed in the V102_03 study. Following is the description of the vaccine groups in the parent study and the vaccines administered in the present study.

ABCWY+OMV: This group received 2 doses of MenABCWY + full dose of outer membrane vesicle (OMV) (25 µg) at 0, 2 month schedule in parent study V102_03. In V102_03E1, this group was further randomized to 2 groups in 1:1 ratio; one group received a third dose of MenABCWY + full OMV and the other group received a placebo. These groups are designated as 2OMV_OMV and 2OMV_Pbo respectively in this report.

ABCWY+qOMV: This group received 2 doses of MenABCWY+ ¼ dose of OMV (6.25 µg) at 0, 2 month schedule in parent study V102_03. In the present extension study V102_03E1, this group was further randomized to 2 groups in 1:1 ratio; one group received a third dose of MenABCWY+ ¼ of OMV and the other group received placebo. These groups were designated as 2qOMV_qOMV and 2qOMV_Pbo respectively in this report.

rMenB+OMV: This group received 2 doses of rMenB+OMV at 0, 2 month schedule in parent study V102_03. In this extension study V102_03E1, this group was further randomized to 2 groups4 in 1:1 ratio; one group received the first dose of MenABCWY + full dose of OMV, and the second group received MenABCWY+ ¼ dose of OMV. These groups were designated as 2B_OMV and 2B_qOMV respectively in this report.

Placebo/ACWY: This group received placebo as vaccination-1 and MenACWY as vaccination-2 at 0, 2-month schedule in V102_03. In this extension study this group was further randomized to 3 groups in 1:1:1 ratio; one group received MenABCWY + full dose of OMV, the second group received MenABCWY+ ¼ dose of OMV and the third group received placebo. These groups were designated as 1M_OMV, 1M_qOMV and 1M_Pbo respectively.

CHMP comment:

It is noted that no subjects received Bexsero during this study.

Results

Approximately 416 subjects that received all required vaccinations and completed the study termination visit in the primary study, V102_03, were to be asked to participate in this extension study. In total 480 subjects were enrolled in V102_03 study, out of which 416 subjects, who were eligible for the extension study were planned to be enrolled into V102_03E1 study. A total of 190 subjects who met all the inclusion criteria were enrolled into V102_03E1.

CHMP comment:

The low number of subjects in each group is noted.

Immunogenicity

As a part of primary objective, the immunogenicity against *N meningitidis* was assessed in terms of percentage of subjects with seroresponse against serogroups A, C, W and Y and HT-hSBA ≥1:5 against serogroup B strains. Overall the immune response against serogroups A, C, W, Y and against serogroup B strains was good at day 30 after MenABCWY booster vaccination in subjects who

previously received the same vaccine formulation in study V102_03 across the vaccine groups (Table 2-5).

A booster dose of MenABCWY in subjects who had previously received MenABCWY or MenACWY or rMenB +OMV resulted in high antibody titers at day 30 against serogroups A, C, W, Y and the serogroup B test strains. Differences in titers observed against serogroup A, C, W, and Y strains between the subjects previously vaccinated with MenACWY or MenABCWY are attributable to the number of doses of vaccine in the primary series: for MenABCWY the subjects in the parent trial received 2 doses whereas MenACWY is a single dose primary series.

Further evaluation of immune response on day 30 in terms of HT-hSBA seroresponse, GMTs and 4-fold increase in HT-hSBA response showed an overall better immune response against most of the serogroup B strains when subjects received rMenB+OMV boosted with full dose of OMV of MenABCWY (2B_OMV).

CHMP comment:

The best immune response to serogroup B strains on day 30 was seen in subjects who received Bexsero during the primary study and then the MenABCWY formulation containing full dose of OMV in the extension study.

At 24 months after primary vaccination, there was a substantial decrease in HT-hSBA response against serogroups A, C, W, Y and serogroup B strains across all the vaccine groups. In comparison to rMenB+OMV group and the MenACWY group, the persistence of immune response at 24 months after primary vaccination was better in MenABCWY group who received full dose of OMV (MenABCWY+OMV) against serogroups C, W, Y. Similarly, for serogroup B strains and serogroup A, the persistence of immune response at 24 months after primary vaccination was observed better in subjects who received rMenB+OMV.

CHMP comment:

It is noted that the persistence of the immune response at 24 months post primary vaccination was better in subjects receiving Bexsero compared to the combination formulations. At 36 months post primary vaccination, the immune response against serogroup B strains were on the same level as baseline in the groups receiving Bexsero in the primary study and thereafter placebo in the extension study. The timely decrease in antibody titers has been previously observed after Bexsero vaccination and might indicate a potential need of a booster dose.

Safety

In total 5 subjects with SAEs and 9 subjects with NOCDs were reported from day 1 through study termination of V102_03E1. According to the investigator, none of the SAEs and NOCDs had any causal relationship with the study vaccination. Between V102_03 and V102_03E1 studies, asthma (4 subjects) was the most frequently reported NOCD followed by rhinitis allergic (2 subjects) and obesity (2 subjects).

CHMP comment:

As Bexsero was not administered during this extension study, it is not possible to draw any conclusions on safety for this vaccine based on these study results. However, no new chronic diseases were considered related to the study vaccination in either the primary or extension studies.

Discussion on immunogenicity and safety

This report contains the clinical study reports of studies V102_03 and V102_03E1. These studies were conducted as part of the development program of the investigational meningococcal combination vaccine MenABCWY, intended to protect against the five most common *Neisseria meningitides*

serogroups (A, B, C, W and Y) responsible for invasive meningococcal disease worldwide. Bexsero was used in study V102_03 as a comparator vaccine, while in study V102_03E1 was evaluated the antibody persistence at 24 months after vaccination performed in study V102_03.

In study V102_03, the secondary immunogenicity objectives compared the immunogenicity of each MenABCWY formulation with that of MenACWY and Bexsero. Immune response in terms of percentages of subjects with hSBA ≥1:5, hSBA ≥1:8, or 4-fold increase in hSBA titer to serogroup B test strains for fHbp, NHBA, NadA, and PorA indicated no notable difference between study formulations MenABCWY+OMV and MenABCWY+qOMV. Responses following vaccination with Bexsero were higher against these test strains than were responses following vaccination with either MenABCWY formulation. Comparison of hSBA GMTs also indicated that the Bexsero vaccine induced a higher immune response than the MenABCWY formulations against all 4 serogroup B test strains. The differences were statistically significant, with the exception of the fHbp strain in the ABCWY+qOMV group.

Reactogenicity profiles of the MenABCWY formulations were comparable to each other and to that of Bexsero. No new safety concerns regarding Bexsero were identified from this study.

In study V102_03E1, a booster dose of MenABCWY in subjects who had previously received MenABCWY, MenACWY or Bexsero resulted in high antibody titers at day 30 against serogroups A, C, W, Y and the serogroup B test strains. The immune response on day 30 in terms of HT-hSBA seroresponse, GMTs and 4-fold increase in HT-hSBA response showed an overall better immune response against most of the serogroup B strains when subjects received Bexsero boosted with full dose of OMV of MenABCWY compared with other combinations. Similarly, for serogroup B strains and serogroup A, the persistence of immune response at 24 months after primary vaccination was observed better in subjects who received Bexsero.

In total 5 subjects with SAEs and 9 subjects with NOCDs were reported from day 1 through study termination of V102_03E1, none of which considered related to study vaccination. Between V102_03 and V102_03E1 studies, asthma (4 subjects) was the most frequently reported NOCD followed by rhinitis allergic (2 subjects) and obesity (2 subjects).

The MAH also submitted the V102_03 Erratum to the CSR. This Erratum was submitted to correct some minor transcription errors affecting the original CSR, which were considered not to impact any of the analyses and interpretations of the study results presented in the original CSR.

3. Rapporteur's overall conclusion and recommendation

Overall conclusion

This article 46 submission is considered satisfactory and no further regulatory action regarding *Bexsero* is required.

Recommendation

☒ Fulfilled:

No regulatory action required.

☐ Not fulfilled: